Examining the relationship between altered brain functional connectome and disinhibition across 33 impulsive and compulsive behaviours

Yann Chye, Chao Suo, Rafael Romero-Garcia, Richard A.I. Bethlehem, Roxanne Hook, Jeggan Tiego, Ian Goodyer, Peter B. Jones, Ray Dolan, Edward T. Bullmore, Jon E. Grant, Murat Yücel and Samuel R. Chamberlain

Impulsive and compulsive problem behaviours are associated with a variety of mental disorders. Latent phenotyping indicates the expression of impulsive and compulsive problem behaviours is predominantly governed by a transdiagnostic ‘disinhibition’ phenotype. In a cohort of 117 individuals, recruited as part of the Neuroscience in Psychiatry Network (NSPN), we examined how brain functional connectome and network properties relate to disinhibition. Reduced functional connectivity within a subnet-work of frontal (especially right inferior frontal gyrus), occipital and parietal regions was linked to disinhibition. Findings provide insights into neurobiological pathways underlying the emergence of impulsive and compulsive disorders.

Keywords
Impulsivity; compulsivity; brain network; connectome; transdiagnostic.

Copyright and usage
© The Author(s), 2021. Published by Cambridge University Press on behalf of the Royal College of Psychiatrists. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

Method
Participants were recruited from a larger cohort of adolescents and young adults from the Neuroscience in Psychiatry Network (NSPN) study. A detailed description of the recruitment methods and sample have been previously published. In brief, the NSPN was set up as a demographically representative sample of the UK population, using a stratified recruitment design. Participants were entered on the basis of having no history of psychiatric treatment or neurological disorder, head injury or intellectual disability. Measures of impulsivity and compulsivity symptoms were collected with the ICBC, 3 years after enrolment. The ICBC assesses for the frequency of 33 common impulsive and compulsive problem behaviours (e.g. washing, smoking, gambling). In a previous paper, confirmatory factor analysis on 654 participants’ ICBC response identified a single latent factor (termed ‘disinhibition’) accounting for around 70% of the variance in participants’ ICBC scores (see Supplementary Table 1 available at https://doi.org/10.1192/bjp.2021.49, for ICBC checklist items and loadings).

Magnetic resonance imaging acquisition and preprocessing
From the original NSPN cohort, a random subset of participants completed neuroimaging, of whom data were available from 117 who had also undertaken the subsequent round collecting the ICBC data. The study was approved by the Cambridge East Research Ethics Committee (approval number 207190), and individuals provided informed consent.
The network-based statistics connectome software package (version 1.2; https://www.nitrc.org/projects/nbs/) was used to assess for association between interregional connectivity matrix and disinhibition scores, controlling for age, gender and IQ. IQ was recorded with the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II). This first included mass univariate testing at each edge, with a primary component-forming threshold of $P < 0.0001$ uncorrected. Each identified component (i.e. topologically connected subnetwork) was then assessed at $10,000$ permutations, using a family-wise error rate-corrected level of $P < 0.05$.

**Graph theory analysis**

Graph theoretic analysis (i.e. modelling the brain network as a graph of interconnected regions/nodes) was further used to examine specific brain connection properties. The Brain Connectivity Toolbox was used, and properties examined include local network properties (nodal degree, normalised betweenness centrality, local efficiency and clustering coefficient) and global network properties (global efficiency and transitivity). These properties were examined across sparsity thresholds of $0.05$ to $0.2$ (at increments of $0.01$). The areas under the curve across the threshold range for the listed properties were computed, and partial correlation was used to determine if any of these network properties were significantly associated with disinhibition, again controlling for age, gender and IQ. Local and global properties were assessed at $P < 0.000154$ and $P < 0.025$, respectively (i.e. Bonferroni-corrected for number of nodes and number of global properties, respectively).

**Results**

The $117$ participants (71 women) had a mean age of $22.6$ (s.d. $2.7$, range $18–28$) years, and mean IQ of $112.5$ (s.d. $10.7$). Disinhibition factor score estimates ranged from $−1.38$ to $2.28$ (mean $0.05$, s.d. $0.81$). Network-based statistics analysis revealed a subnetwork of $15$ edges across $15$ regions, which was significantly negatively associated with disinhibition scores (family-wise error rate-corrected $P = 0.0203$). The connections primarily linked the right inferior frontal brain region (right pars opercularis) to bilateral lateral occipital regions (9 out of $15$ connections/edges), and the right lateral occipital region to the right parietal (supramarginal) region (4 edges). Two other edges connect the right pars opercularis to the left precentral and left superior frontal gyri. See Fig. 1 for brain networks, visualised with BrainNet Viewer (version 1.7 for MacOS; https://www.nitrc.org/projects/bnv/). Examination of local (all $P > 0.00039$, $r < 0.32$) and global ($all P > 0.016, r < 0.23$) network metrics revealed no other significant association between network measures and disinhibition scores, at the Bonferroni correction threshold.

**Discussion**

This study demonstrates connectome-level variation in brain functional networks associated with disinhibition, providing the first evidence of common functional substrates contributing to both impulsive and compulsive behaviour problems. Reduced network connections across a subnetwork of frontal (specifically right inferior frontal), parietal and occipital regions were observed in association with increased disinhibition. Over half of the affected edges connect the bilateral occipital regions to the right inferior frontal region – specifically, the pars opercularis. These changes were regionally specific and did not reflect changes in global network properties. These data indicate that variation in connectivity is related to disinhibition, which was driven primarily by connection...
to the inferior frontal region (as measured by total number of connecting edges). This converges with other studies emphasising the central role of the inferior frontal brain region in response inhibition and maladaptive behavioural problems.10 The inferior frontal and occipital cortices are co-activated, and show marked functional coupling when inhibitory control is required.11 Additionally, reduced inhibition-related functional connectivity between frontal and posterior brain regions constitutes a candidate vulnerability marker for obsessive–compulsive disorder.12 The current data suggest that aberrant long-distance resting-state connections along the anterior-posterior axis may play a role in predisposing toward disinhibited behaviour.

**Limitations and conclusion**

The original NSPN cohort was recruited to be epidemiologically representative of the general UK population. This reduces selection biases inherent in clinical samples, but may limit the applicability of findings to those with more severe psychopathology (i.e. higher disinhibition). Another limitation is that the study shows association not causality. Future work should examine what precise underlying mechanisms (psychological and biological) contribute to the observed link between disinhibition and brain dysconnectivity. However, our findings provide insights into neurobiological processes that confer vulnerability to many types of problematic impulsive and compulsive behaviours, and therefore may be relevant to the search for transdiagnostic heuristics. Extending these techniques into patient populations, and larger imaging cohorts, will ideally refine our current understanding of the aetiology and course of psychiatric disorders, and the role of common latent phenotypes in the emergence of psychiatric conditions. This will require the inclusion of appropriate measurement tools for impulsivity and compulsivity in large-scale population studies, which have typically overlooked such dimensional measures in favour of binary measures or interrogations of symptoms of discrete disorders (e.g. obsessive–compulsive disorder).

**Author contributions**

R.R-G., R.A.J.B., R.H., I.G., P.B.J., R.D., E.T.B., J.E.G., M.Y. and S.R.C. were responsible for study conceptualisation and data collection. J.T., Y.C., M.Y. and S.R.C. were responsible for study design and conceptualisation, specific research question and contributed to the interpretation of data. Y.C., C.S., R.R.G. and I.T. conducted the analysis. Y.C. drafted the paper, with support and input from all authors.

**Funding**

This research was funded by a clinical fellowship from the Wellcome Trust to S.R.C. (reference 110049/2/15/Z/8/4). The study was supported by the Neuroscience in Psychiatry Network, a strategic award from the Wellcome Trust to the University of Cambridge and University College London (reference 095844/1/11/Z), and by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (Mental Health).

**Declaration of interest**

Y.C. was supported by National Health and Medical Research Council (NH&MRC) project grant 1139979. R.R.-G. was funded by a Guarantors of Brain fellowship. E.T.B. is an NIHR Senior Investigator. R.A.J.B. was funded by a British Academy postdoctoral fellowship. S.R.C. consults for teso Digital Health, and receives stipends from Elsevier for editorial work at Comprehensive Psychiatry and Neuroscience & Biobehavioral Reviews. J.E.G. has received research grants from the National Institute on Drug Abuse (NIDA), National Center for Responsible Gaming, American Foundation for Suicide Prevention, Forest Pharmaceuticals and Roche Pharmaceuticals; receives yearly compensation from Springer Publishing for acting as Editor-in-Chief of the Journal of Gambling Studies; and has received royalties from Oxford University Press, American Psychiatric Publishing, Norton Press, Johns Hopkins University Press and McGraw Hill. J.T. was supported by NH&MRC project grants 1002458 and 1046054. I. G. consults for Lundbeck; is supported by a Wellcome Trust Strategic Award; and is Chairperson and scientific advisor to the Peter Cundall Centre for Youth Depression Research, Centre for Addictions and Mental Health, University of Toronto. E.T.B. is a member of the Sose Heptanes scientific advisory board and is a National Institute of Health Research Senior Investigator. M.Y. has received funding from Monash University and Australian Government funding bodies such as the NH&MRC (including fellowship APP1117188), the Australian Research Council, Australian Defense Science and Technology, and the Department of Industry, Innovation and Science. He has also received philanthropic donations from the David Winston Turner Endowment Fund and the Wilson Foundation; and payment from law firms in relation to court, expert witness and/or expert review reports. The funding sources had no role in the design, management, data analysis, presentation, interpretation or write-up of the data. The other authors report no disclosures or potential conflicts of interest.

**References**


**Supplementary material**

To view supplementary material for this article, please visit https://doi.org/10.1192/bjp.2021.49

**Data availability**

The data that support the findings of this study are available from the corresponding author, Y.C., upon reasonable request.